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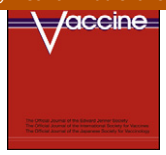

Brief report

# The safety and effectiveness of self-administration of intranasal live attenuated influenza vaccine in adults☆

Christopher S. Ambrose*, Xionghua Wu

*MedImmune, LLC, Gaithersburg, MD, USA*

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ABSTRACT

Intranasal live attenuated influenza vaccine (LAIV) has potential for self-administration (SA) by adults and adolescents, which could save time and cost in mass vaccination settings. Participants in a study of LAIV in adults ($n = 4561$) selected either SA or health care provider (HCP) administration and were followed for febrile illness during the influenza season. More LAIV recipients chose SA-LAIV (72%) than HCP-LAIV (28%). Overall, 97% of SA-LAIV and 98% of HCP-LAIV recipients had no problems with vaccine administration. Four of 13 study sites enrolled more than 50 subjects in both cohorts. Overall and for these 4 sites, illness incidence was similar with SA-LAIV and HCP-LAIV. Solicited reactogenicity events and adverse events through 7 days post vaccination were comparable for SA-LAIV and HCP-LAIV recipients; both groups exhibited increased runny nose, sore throat, and cough relative to placebo recipients. SA-LAIV and HCP-LAIV appeared similarly effective against influenza-like illness and had comparable safety profiles.



## 1. Introduction

Influenza vaccine delivery requires vaccinating a large population within a short time frame each year. Like other influenza vaccines, intranasal live attenuated influenza vaccine (LAIV) is currently approved for administration by health care professionals (HCP); however, for adults and adolescents, self-administration (SA) could be more efficient and less costly. These efficiencies could be particularly important in urgent mass vaccination settings, such as in response to a severe influenza epidemic or an influenza pandemic.

In 1997–1998, a randomized, placebo-controlled study was conducted to evaluate the effectiveness of LAIV in preventing influenza-like illness in U.S. adults 18–64 years of age [1]. As part of the study protocol, subjects were allowed to choose between supervised self-administration and HCP administration. The objective of the current analysis was to analyze the effectiveness and safety of SA-LAIV compared with HCP-LAIV.

## 2. Methods

### 2.1. Study design

The details of the original study methods have been described previously [1]. Briefly, 4561 adults 18–64 years of age were randomized 2:1 to receive LAIV or placebo at 13 sites across the United States and were followed during the influenza season for the incidence of influenza-like illness. Subjects with high-risk medical conditions were excluded and randomization was balanced by site. The primary endpoint was the incidence of any febrile illness (AFI) during the influenza season. AFI constituted ≥2 consecutive days of symptoms with ≥1 day of fever or ≥2 symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness) on ≥1 day. Secondary endpoints included severe febrile illness (SFI, ≥3 consecutive days of symptoms, ≥1 day of fever, and ≥2 symptoms on ≥3 days) and febrile upper respiratory illness (FURI, ≥2 consecutive days of upper respiratory tract symptoms, ≥1 day of fever, and 2 symptoms on ≥1 day). Specimens for laboratory identification of influenza and vaccine immunogenicity were not collected. Post vaccination reactogenicity symptoms and other unsolicited adverse events (AEs) were collected by diary for 7 days following vaccination. After receiving a single page of written administration instructions (see Supplementary Fig.), each participant selected either SA or HCP administration.

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* Corresponding author at: MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878, USA. Tel.: +1 301 398 4454; fax: +1 301 398 9454.
*E-mail address:* ambrosec@medimmune.com (C.S. Ambrose).

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### 2.2. Statistical analysis

The proportion of subjects selecting SA versus HCP administration was calculated overall and by site. The analysis population consisted of subjects who received LAIV and had evaluable data for AFI, SFI, and FURI. The effectiveness of SA-LAIV relative to HCP-LAIV was evaluated descriptively for sites with significant enrollment in both groups. Using data from all sites, multiple variable logistic regression analysis was conducted to compare the proportion of SA-LAIV and HCP-LAIV recipients experiencing AFI, SFI, and FURI. Exploratory variables included age (<40 vs. ≥40 years), gender, race (white vs. other), high risk (yes vs. no), and study site. The log of the observation days was used as the offset variable. Safety was assessed by comparing solicited reactogenicity events (REs) and other AEs, including epistaxis events, within 7 days of vaccination.

## 3. Results

Overall, 72% of LAIV recipients chose SA-LAIV ($n = 2026$) and 28% chose HCP-LAIV ($n = 805$). Self-administration was chosen more frequently by younger subjects; 59% of SA-LAIV versus 48% of HCP-LAIV subjects were <40 years of age ($P < 0.001$), and 87% and 83% of SA-LAIV and HCP-LAIV subjects, respectively, were white ($P < 0.003$). SA-LAIV subjects had a longer duration of surveillance during site-specific influenza outbreak periods (47 vs. 44 days; $P < 0.001$; Table 1). Across sites, the proportion of subjects selecting self-administration varied considerably, ranging from 0 to >99%. Four of 13 study sites (sites 1, 5, 9, and 11) enrolled >50 subjects under both administration methods. Overall, 96.7% and 98.3% of SA-LAIV and HCP-LAIV subjects, respectively, had no problems with vaccine administration.

Across all study sites, without adjustment for confounders, illness rates were comparable for SA-LAIV and HCP-LAIV recipients, although rates trended lower among HCP-LAIV recipients: AFI incidence was 13.5% vs. 12.3% for SA-LAIV and HCP-LAIV, respectively; SFI incidence was 10.2% vs. 9.8%; FURI incidence was 8.6% vs. 8.2%. Among the 4 study sites that enrolled more than 50 subjects under both administration methods (SA-LAIV, $n = 762$; HCP-LAIV, $n = 455$), rates of AFI, FURI, and SFI during site-specific influenza outbreak periods were similar for SA-LAIV subjects and HCP-LAIV subjects (Fig. 1).

Using logistic regression to adjust data from all study sites for potential confounding variables, the incidence of illness was not statistically significantly different between SA-LAIV and HCP-LAIV subjects. For AFI, the odds ratio for HCP-LAIV vs. SA-LAIV was 1.01 (95% CI: 0.75, 1.35). For SFI and FURI, the odds ratios were 0.96 (95% CI: 0.69, 1.34) and 0.93 (95% CI: 0.65, 1.32), respectively.

Rates of reactogenicity events were comparable among SA-LAIV and HCP-LAIV subjects (Table 2). For both groups, the largest rate increases relative to placebo were observed for runny nose and sore throat. The rate of runny nose was higher in HCP-LAIV versus SA-LAIV recipients ($P = 0.04$). Regardless of treatment or administration group, higher rates of reported runny nose, sore throat, headache, chills, and tiredness/weakness were observed among female subjects ($P < 0.001$ for all). Other unsolicited AEs were reported in 31.4% of SA-LAIV and 29.9% of HCP-LAIV subjects ($P = 0.47$). Few cases of epistaxis were reported, and rates of epistaxis were comparable for SA-LAIV (0.3%) and HCP-LAIV (0.2%) recipients.

**Table 1**
Characteristics of LAIV recipients by administration method.

| Characteristic | SA-LAIV ($n = 2026$) | HCP-LAIV ($n = 805$) | $P$ value* |
|---|---|---|---|
| Age group, $n$ (%) | | | |
| <40 years | 1202 (59) | 389 (48) | <0.0001 |
| ≥40 years | 824 (41) | 416 (52) | – |
| Sex, $n$ (%) | | | |
| Male | 919 (45) | 336 (42) | 0.0802 |
| Female | 1107 (55) | 469 (58) | – |
| Race, $n$ (%) | | | |
| White | 1767 (87) | 667 (83) | 0.0026 |
| Other | 259 (13) | 138 (17) | – |
| Subjects with high-risk underlying medical conditions, $n$ (%) | | | |
| Yes | 15 (1) | 6 (1) | 0.9889 |
| No | 2011 (99) | 799 (99) | – |
| Investigator site, $n$ (%) | | | |
| 1 | 202 (10) | 159 (20) | <0.0001 |
| 2 | 108 (5) | 45 (6) | – |
| 3 | 0 (0) | 98 (12) | – |
| 4 | 26 (1) | 1 (0) | – |
| 5 | 286 (14) | 120 (15) | – |
| 6 | 206 (10) | 2 (0) | – |
| 7 | 344 (17) | 31 (4) | – |
| 8 | 217 (11) | 1 (0) | – |
| 9 | 139 (7) | 85 (11) | – |
| 10 | 184 (9) | 30 (4) | – |
| 11 | 135 (7) | 91 (11) | – |
| 12 | 31 (2) | 130 (16) | – |
| 13 | 148 (7) | 12 (1) | – |
| Observation days, mean (SD) | 47 (11.4) | 44 (9.4) | <0.0001 |

HCP, healthcare professional; LAIV, live attenuated influenza vaccine; SA, self-administered.

* $P$ value represents the comparison between SA-LAIV and HCP-LAIV using $t$ test for observation days and chi-square test for others.

## 4. Discussion

This nonrandomized comparison of SA-LAIV and HCP-LAIV suggests that both administration methods were similarly effective. Most study participants chose self-administration, and few problems were reported. Reactogenicity events were similar in both groups, with comparable increases in runny nose and sore throat among LAIV recipients compared with placebo recipients. The rate of runny nose was higher with HCP-LAIV versus SA-LAIV, likely reflecting underlying differences in the 2 populations. In

**Table 2**
Reactogenicity events following vaccination among LAIV recipients by administration method relative to placebo recipients.

| Reactogenicity event | Number of reactogenicity events, $n$ (%) | | |
|---|---|---|---|
| | SA-LAIV ($n = 2026$) | HCP-LAIV ($n = 805$) | Placebo ($n = 1420$) |
| Runny nose | 869 (42.9)* | 380 (47.2)*,† | 372 (26.2) |
| Headache | 795 (39.2) | 312 (38.8) | 535 (37.7) |
| Sore throat | 523 (25.8)* | 217 (27.0)* | 229 (16.1) |
| Tiredness/weakness | 494 (24.4)* | 189 (23.5) | 287 (20.2) |
| Muscle aches | 307 (15.2) | 138 (17.1) | 203 (14.3) |
| Cough | 274 (13.5)* | 104 (12.9)* | 139 (9.8) |
| Chills | 159 (7.8) | 66 (8.2) | 88 (6.2) |
| Fever (oral temperature >100 F) | 25 (1.2) | 8 (1.0) | 17 (1.2) |

HCP, healthcare professional; LAIV, live attenuated influenza vaccine; SA, self-administered.

* $P < 0.05$ vs. placebo.

† $P = 0.04$ for HCP-LAIV vs. SA-LAIV.

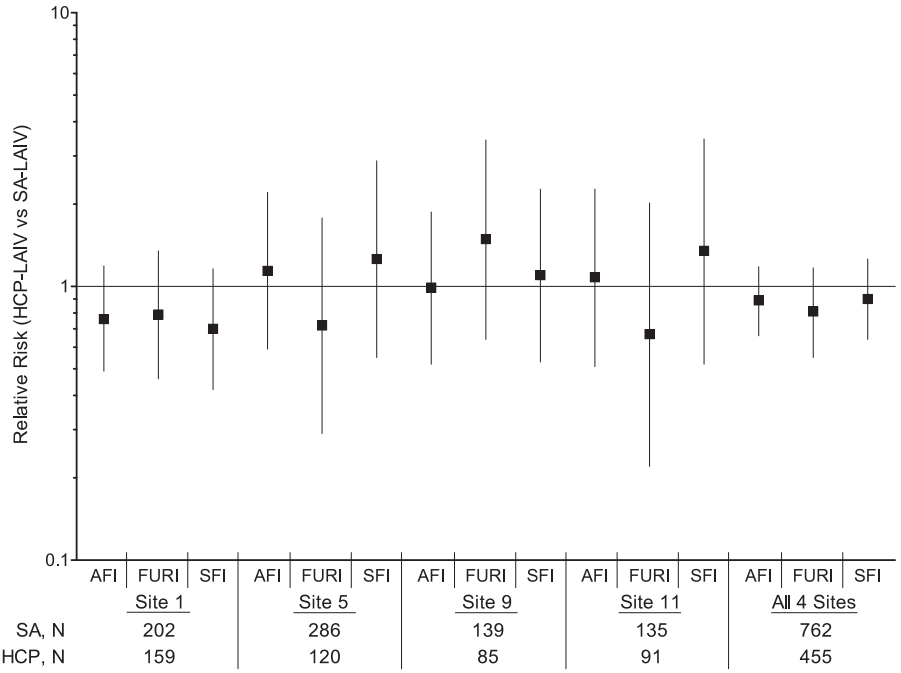


**Fig. 1.** Relative risk of influenza-like illness for HCP-LAIV vs. SA-LAIV by site. AFI = any febrile illness; FURI = febrile upper respiratory illness; HCP = healthcare professional; LAIV = live attenuated influenza vaccine; SA = self-administered; SFI = severe febrile illness. Symbol represents point estimate of the relative risk; lines represent 95% CIs.

particular, more female subjects chose HCP administration, and female subjects were more likely to report runny nose regardless of administration method. Increased vaccine reactogenicity among adult women has been observed previously with LAIV [2] and other vaccines [3–6]. Overall, reactogenicity profiles of SA-LAIV and HCP-LAIV are consistent with comparable vaccine-induced immune responses in each group. However, randomized comparisons of the effectiveness or immunogenicity of self-administration and HCP administration methods are needed to support routine self-administration of LAIV.

The feasibility of LAIV self-administration was examined in a study by the Kentucky Department of Health (Louisville, KY) [7] in 2009. In a community walk-in immunization clinic, participants self-immunized in groups of 4–15 individuals after a short educational presentation by a nurse. A maximum of 124 individuals were immunized in 3 h. Two patients were not able to self-vaccinate due to an anxiety disorder and a mild neuromuscular disorder. Side effects were reported by 2.7% of vacinees, and no serious side effects occurred. Among self-vaccinated individuals, 97% felt they used the vaccine correctly, and 96% stated that they would self-administer LAIV in the future [7].

Self-administration has also been evaluated for intradermal inactivated influenza vaccine. Coleman et al. randomized 228 adults 18–59 years to supervised self-administration versus nurse administration [8]. Successful administration on first attempt was reported for 93% of those self-administering, with 42% preferring self-administration in the future. Hemagglutination inhibition titers 21 days following vaccination were similar in both groups, and less pain was reported by subjects who self-administered [8].

In this study, self-administration was performed under the direct supervision of study staff. Supervised self-administration ensures proper education on administration techniques and appropriate responses to any immediate adverse reactions, such as hypersensitivity reactions. The prescribing information for LAIV [9] states that "appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine." Anaphylaxis and serious hypersensitivity following LAIV have been rare with <1 report per million doses with >50 million doses administered between 2003 and 2012. Nevertheless, anaphylactic reactions are possible and appropriate medical treatment should be available. For other disease conditions that require treatment by injectable medications, such as diabetes and rheumatoid arthritis, home self-administration has become the standard of care [10–12]. However, unsupervised self-administration is recommended to be initiated only after HCP education on self-administration, potentially with an initial in-office administration.

There was significant variation across study sites in the proportion of subjects who elected self-administration. This variability is likely due to the manner in which site staff presented the option to study participants. Despite this variability, the high proportion that selected self-administration overall suggests a preference for self-administration compared with administration by a HCP.

The primary limitation of the current analysis was the lack of randomization of study subjects to SA-LAIV and HCP-LAIV. Because of this limitation, there were significant differences in SA-LAIV and HCP-LAIV subjects, and analyses of AFI, SFI, and FURI incidence by administration method had to be adjusted for potential confounding variables. Differences due to study site were controlled in the analysis through the exclusion of sites with fewer than 50 subjects in each group; controlling for geographic location helped to minimize bias due to local variability in respiratory virus activity. The logistic regression analysis across all sites permitted adjustment for study site and other confounding variables. Additionally, the lack of laboratory confirmation of influenza prevented an analysis of influenza-specific illness.

## Contributors

Drs. Ambrose and Wu contributed to the study concept and design, acquisition, analysis and interpretation of data, drafted the manuscript, and were involved in the editing and critical review of all the contents. Statistical analysis was performed by Dr. Wu. Both authors approved the final manuscript for submission.

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## Role of the sponsor

All authors are employees of MedImmune who worked collaboratively in the design of the analysis and interpretation of the data and reviewed and approved the manuscript.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.12.028.

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